BIOGRAPHICAL SKETCH

NAME: McGinnis, Christopher Swart

eRA COMMONS USER NAME: cmcginnis92

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	COMPLETION	FIELD OF STUDY
Wesleyan University; Middletown, CT	BA	05/2014	Biology, Biochemistry, Science in Society Program
University of California, San Francisco; San Francisco, CA	MA PhD	09/2018 09/2021	Cell Biology, Genomics, Biotechnology, Bioinformatics
Stanford University; Palo Alto, CA	Postdoc	Ongoing	Immunology, Cancer Biology, Genomics, Bioinformatics

A. Personal Statement

My long-term research interests are focused on understanding tumor-immune interactions during metastasis. Beyond answering fundamental questions in the field of cancer immunology, I hope to improve human health by developing the **first-generation of anti-metastatic immunotherapies.** Such an achievement would address unmet therapeutic needs for the 50-90% of cancer patients who succumb to metastatic disease. My approach is uniquely interdisciplinary, spanning the fields of cancer immunology, bioengineering, and genomics. Specifically, I intend to link longitudinal single-cell analysis, chemical compound screens, and cancer immunology approaches to uncover mechanisms of pro-metastatic immune reprogramming and provide insight into how to halt or reverse metastatic progression. Noting these interests and goals, **I plan to pursue these directions as a full-time academic researcher.**

My research interests are largely inspired by my education and training which have provided me with a deep understanding of genomics, bioengineering, immunology, cancer biology, and bioinformatics. I have received formal training in both wet- and dry-lab sciences during my undergraduate and graduate education, and as a PhD student in Dr. Zev Gartner's lab at UCSF, **I completed my dissertation with support from an F31 Predoctoral Fellowship Award from the NCI.** At UCSF, my research focused on computational (McGinnis, *et al., Cell Systems*, 2019) and molecular (McGinnis*, Patterson*, *et al., Nature Methods*, 2019) single-cell genomics method development. Moreover, through collaborative work at UCSF and Caltech, I built my foundation in immunology (McGinnis, *et al., BMC Biology*, 2021), metastasis biology (Winkler, Tan, Diadhiou, McGinnis, *et al., BioRxiv*, 2023), and high-throughput screening (Jiang*, Chen*, Tsou, McGinnis, *et al., BioRxiv*, 2023) which inspire my current research interests.

After completing my PhD, I joined Dr. Ansu Satpathy's group at Stanford University where I study tumor-immune interactions in metastasis with independent research support from the Cancer Research Institute and the Parker Institute for Cancer Immunotherapy. My time at Stanford has been critical for my growth as a scientist as I have received world-class mentorship in cancer immunology and bioinformatics, while simultaneously having access to resources that enabled me to build a comprehensive longitudinal single-cell atlas of immune cells in the lung metastatic microenvironment (McGinnis, *et al., BioRxiv*, 2023) and develop an *ex vivo* lung culture platform for high-throughput chemical compound screens.

I now seek the support of the K99/R00 Pathway to Independence Award, which will provide critical opportunities for mentored training and skill development and enable me to transition into a fully independent investigator.

B. Positions and Honors

Positions & Employments

2021-present	Postdoctoral Fellow, Department of Pathology, Stanford University; Palo Alto, CA. Mentor: Ansuman Satpathy, MD, PhD.
2017-2020	Biochemistry Instructor, Post-Baccalaureate Program, UCSF School of Medicine; San Francisco, CA. Mentor: Valerie Margol, MA.
2016-2021	Graduate Student, Tetrad Graduate Program, Department of Pharmaceutical Chemistry, UCSF; San Francisco, CA. Mentor: Zev Gartner, PhD.
2014-2016	Research Associate, Institute for Systems Biology; Seattle, WA. Mentors: Leroy Hood, MD, PhD and Sui Huang, MD, PhD.
2012-2014	Teaching Assistant, Department of Molecular Biology & Biochemistry, Wesleyan University; Middletown, CT. Mentor: Robert Lane, PhD.
2013	Summer Research Fellow, Department of Genetics and Genome Sciences, University of Connecticut School of Medicine; Farmington, CT. Mentor: Andrew Arnold, MD.
2011-2013	Undergraduate Research Assistant, Department of Biology, Wesleyan University; Middletown, CT. Mentor: Ann Burke, PhD.

Honors & Awards

2016	Matilda Edlund Scholarship (finalist)
2016	National Science Foundation Graduate Research Fellowship Program (honorable mention)
2019	Keystone Symposium Future of Science Fellowship
2019	UCSF Program for Breakthrough Biomedical Research
2019	UCSF Catalyst Award
2019	Mary Anne Kota Kimble Seed Award for Innovation
2019	ARCS Foundation Scholar
2021	Society for Laboratory Automation and Screening Innovation Award
2021	National Cancer Institute Ruth L. Kirschstein National Research Service Award (F31)
2021	Harold M. Weintraub Graduate Student Award (nominated)
2021	Cancer Research Institute Irvington Postdoctoral Fellowship Award
2023	Parker Institute for Cancer Immunotherapy Scholar Award

Invited Oral Presentations

12/18, 12/20	Bay Area RNA Club Annual Symposium
01/19, 05/20	Keystone Symposium: Single Cell Biology
06/19	Brotman-Baty Institute Single-Cell Symposium
04/20	Cell Symposium: The Conceptual Power of Single-Cell Biology
10/20	Illumina Single-Cell Sequencing Virtual Symposium – Bay Area
04/21	Cold Spring Harbor Laboratory Conference: Systems Immunology
10/22	Wesleyan University Biochemistry Seminar Series
05/23	Keystone Symposium: Metastasis
09/23	Medical University of Vienna Cancer Research Seminar Series

C. Contributions to Science

A full list of my peer-reviewed manuscripts is available on Google Scholar. *denotes equal contribution

C1. Characterization of pro-metastatic immune reprogramming

Cancer metastasis requires systematic and dynamic remodeling of the immune system in the primary tumor microenvironment, secondary lymphoid organs, bone marrow, and other distant organ sites. Despite the importance of capturing how pro-metastatic immune remodeling occurs over time and space, single-cell genomics analyses aiming to uncover the tumor-immune interactions driving metastasis have primarily

employed cross-sectional designs at disease endpoints. To address this knowledge gap, I have generated and analyzed single-cell genomics datasets which measure the temporal progression of lung immune remodeling in the PyMT breast cancer mouse model [1], as well as differences in the lung and primary tumor microenvironments in patient-derived xenograft breast cancer models which have differential metastatic potential [2]. These datasets have provided insights into novel mechanisms of pro-metastatic immune remodeling during breast cancer metastasis to the lung and have the potential to improve our understanding of metastatic cancer immunology, writ large.

[1] **McGinnis CS**, et al. “The temporal progression of immune remodeling during metastasis.” bioRxiv (2023)
[2] Winkler J, Tan W, Diadhiou CMM, **McGinnis CS**, et al. “Dissecting the contributions of tumor heterogeneity on metastasis at single-cell resolution”. *bioRxiv* (2022).

C2. Single-cell genomics computational doublet detection.

The single-cell genomics field took a dramatic step forward in 2015 with the advent of droplet microfluidics for high-throughput single-cell RNA-sequencing (scRNA-seq). This technological innovation increased the cell-throughput of scRNA-seq by 2-3 orders of magnitude, enabling entirely new kinds of biological questions to be addressed at single-cell resolution. More recently, droplet microfluidics applications have also been developed for single-nucleus assay for transposase-accessible chromatin using sequencing (snATAC-seq). One known caveat of droplet microfluidics, however, is that Poisson loading of cells or nuclei into emulsion oil droplets results in a significant proportion of droplets being loaded with >1 cell/nucleus. These technical artifacts are known as ‘doublets’ and can confound scRNA-seq and snATAC-seq data analysis by appearing as ‘hybrid’ or ‘intermediate’ cell states that do not exist.

I solved this issue by developing DoubletFinder [1], which was the first computational method for systematic doublet identification in scRNA-seq data. DoubletFinder finds doublets using a nearest-neighbors approach by identifying cells which preferentially co-localize in gene expression space with artificial doublets generated by averaging the expression profiles of random cell pairs. DoubletFinder has been broadly implemented by the single-cell genomics community and has even inspired the development of complementary methods which I have been invited to review. My specific role in the DoubletFinder project involved conceiving and implementing the method, performing bioinformatics analyses, and writing the manuscript.

One caveat with DoubletFinder and other community-detection based doublet detection algorithms is that they perform sub-optimally on snATAC-seq data. In contrast, doublet detection methods such as AMULET [2] which leverage the trinary nature (0, 1, or 2) of snATAC-seq data to identify doublets as nuclei with elevated levels of bi-allelic read counts, perform better in this context. I contributed to the development of AMULET by performing bioinformatic analyses on snATAC-seq data I generated to benchmark AMULET doublet prediction accuracy.

[1] **McGinnis CS**, Murrow LM, Gartner ZJ. “DoubletFinder: doublet detection in single-cell RNA sequencing data using artificial nearest neighbors.” *Cell Systems* (2019). PMID: 30954475.
[2] Thibodeau A*, Eroglu A*, **McGinnis CS**, et al. “AMULET: a novel read count-based method for effective multiplet detection from single nucleus ATAC-seq data.” *Genome Biology* (2021). PMID: 34465366.

C3. Single-cell genomics sample multiplexing

Since scRNA-seq was developed in early 2010s, it has predominantly been used to perform descriptive analyses of biological systems. For example, numerous ‘Cell Atlas’ research programs are currently underway, which involve sequencing millions of cells spanning a variety of tissues and organ systems in diverse organisms. These efforts are undeniably important, as they will significantly update the cellular ‘parts-lists’ first canonized using anatomical and histological observations. However, in order to employ scRNA-seq for mechanism/hypothesis testing, existing scRNA-seq cell-throughput capabilities must be leveraged in a fashion that enables large numbers of distinct samples (e.g., donors, time-points, replicates, etc.) to be processed in a pooled format. Until recently, this has been largely impossible due to technical constraints of droplet micro-fluidics devices and high reagents costs.

*I solved this issue by developing MULTI-seq [1], a method for scRNA-seq **s**ample **m**ultiplexing **u**sing **l**ipid-**t**agged **i**ndices.* MULTI-seq is currently one of a family of scRNA-seq sample multiplexing technologies which involve labeling plasma membranes with sample-specific DNA barcodes prior to single-cell isolation. By 'tagging' cells before isolation, cells from distinct samples can be processed in a pooled rather than parallel format, resulting in dramatically reduced reagent costs, increased cell-throughput, and improvements in data quality. MULTI-seq is unique amongst other sample multiplexing methods due to its universality – i.e., MULTI-seq will work on all biological entities with a lipid bilayer, enabling its application to cells and nuclei from any species. We leveraged this feature to analyze human metastases and mouse immune cells in the metastatic niche of a patient-derived xenograft mouse model of breast cancer – experiments which first inspired my interests in cancer immunology and metastasis biology.

Since its publication, MULTI-seq has been widely adopted by the single-cell genomics community, resulting in numerous collaborations, invitations for peer-review, and future research directions. For example, I adapted MULTI-seq for snATAC-seq, developing one of the first sample multiplexing tool for this assay called MULTI-ATAC-seq [2]. Moreover, through collaboration with Dr. Matt Thomson's lab at Caltech, I leveraged MULTI-seq to perform one of the first-ever scRNA-seq-coupled high-throughput chemical compound screens. Specifically, we used MULTI-seq to analyze the transcriptional responses of >500 drug compounds in resting and stimulated primary human immune cells. These data highlight the primary modes of immunomodulation in lymphocytes and myeloid cells during an acute inflammatory response, illustrate how scRNA-seq can detect off-target drug activities, and identify previously-unknown drug activities [3].

[1] **McGinnis CS**,* Patterson DM*, et al. "MULTI-seq: sample multiplexing for single-cell RNA sequencing using lipid-tagged indices." *Nature Methods* (2019). PMID: 31209384.

[2] **McGinnis CS***, Conrad DN*, et al. "MULTI-ATAC-seq: sample multiplexing for single-cell ATAC sequencing." In preparation.

[3] Jiang J*, Chen S*, Tsou T, **McGinnis CS**, et al. "D-SPIN constructs gene regulatory network models from multiplexed scRNA-seq data revealing organizing principles of cellular perturbation response." *bioRxiv* (2023).

C4. Single-cell genomics community contribution through MULTI-seq collaborations

In order to make MULTI-seq available to the global scientific community, I established a pipeline for distributing MULTI-seq reagents, protocols, and bioinformatics tools to interested users, free of charge. *During my time at UCSF, I sent MULTI-seq materials to >350 academic and industry labs across 21 different countries and consulted on study design, sample preparation protocols, and bioinformatics troubleshooting with a significant portion of these users*. Moreover, I directly collaborated with researchers at UCSF and beyond on a variety of projects leveraging MULTI-seq. For example, I helped develop a novel method for spatial transcriptomics called ZipSeq which leverages MULTI-seq technology [1], and led a study that demonstrated that scRNA-seq sample-multiplexing of immune cells from unique donors does not cause alloreactivity [2].

For many other cited projects (listed in order of personal contribution), I aided in MULTI-seq experimental execution and design and bioinformatics analyses [3-8].

[1] Hu KH, Eichorst JP, **McGinnis CS**, et al. "ZipSeq: Barcoding for Real-time Mapping of Single Cell Transcriptomes." *Nature Methods* (2020). PMID: 32632238.

[2] **McGinnis CS**, et al. "No detectable alloreactive transcriptional responses during donor-multiplexed single-cell RNA sequencing of peripheral blood mononuclear cells." *BMC Biology* (2021). PMID: 33472616.

[3] Murrow LM, Weber RJ, Caruso JA, **McGinnis CS**, et al. "Mapping hormone-regulated cell-cell interaction networks in the human breast at single-cell resolution." *Cell Systems* (2022). PMID: 35863345.

[4] Zwick RK, Kasparek P*, Palikuqi B*, Viragova S*, Weichselbaum L*, **McGinnis CS***, et al. "Epithelial zonation along the mouse and human small intestine defines five discrete metabolic domains." *Nature Cell Biology* (2023). *In press*.

[5] Huycke TR, Miyazaki H, Häkkinen T, Srivastava V, Barruet E, **McGinnis CS**, et al. "Patterning and folding of intestinal villi by active mesenchymal dewetting." *bioRxiv* (2023).

[6] Yang D, Jones MG, Naranjo S, Rideout III WM, Min KHJ, Ho R, Wu W, Replogle JM, Page JL, Quinn JJ, Horns F, Qiu X, Chen MZ, Freed-Pastor WA, **McGinnis CS**, et al. “Lineage tracing reveals the phylodynamics, plasticity, and paths of tumor evolution.” *Cell*. (2022). PMID: 35523183.

[7] Popova G, Soliman SS, Kim CN, Keefe MG, Hennick KM, Jain S, Li T, Tejera D, Shin D, Chhun BB, **McGinnis CS**, et al. “Human microglia states are conserved across experimental models and regulate neural stem cell responses in chimeric organoids.” *Cell Stem Cell* (2021). PMID: 34536354.

[8] Su-Feher L, Rubin AN, Silberberg SN, Catta-Preta R, Lim KJ, Ypsinalti AR, Zdilar I, **McGinnis CS**, et al. “Single cell enhancer activity distinguishes GABAergic and cholinergic lineages in embryonic mouse basal ganglia.” *PNAS* (2022). PMID: 35377797.

D. Research Support

Ongoing Research Support

Irvington Postdoctoral Fellowship, Cancer Research Institute McGinnis (PI) 01/2022–01/2025
Interrogating Immunomodulation for Anti-Metastatic Therapy
The goals of this project are to (1) construct a longitudinal single-cell ‘atlas’ of the lung in PyMT mice over the course of metastatic progression and (2) perform high-throughput chemical compound screens to identify candidates for the first generation of anti-metastatic immunotherapies.
Role: PI
Funding: $186,000

PICI Scholar, Parker Institute for Cancer Immunotherapy McGinnis (PI) 01/2023–01/2025
Interrogating Immunomodulation for Anti-Metastatic Therapy
The goal of this project is as described above.
Role: PI
Funding: $195,025

Completed Research Support

National Cancer Institute F31 CA257349-0 McGinnis (PI) 09/2020–09/2021
Interrogating Immunomodulation for Anti-Metastatic Therapy
The goal of this project is as described above. The award was terminated early as I sought out a new academic environment for my postdoctoral studies that was better tailored to the stated research objectives.
Role: PI
Funding: $36,252

Achievement Rewards for College Scientists Scholarship McGinnis (PI) 06/2019–06/2020
Combating Hirschsprung’s Disease with Highly Multiplexed Single-Cell Transcriptomics
The goal of this project was to perform MULTI-seq chemical compound screens using an *in vitro* system of iPSC-derived enteric neurons in order to find novel therapies for treating Hirschsprung’s Disease.
Role: PI
Funding: $15,000